Allogeneic and autologous serum eye drops: a pilot double-blind randomized crossover trial

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ABSTRACT.

Purpose: Serum eye drops (SEDs) are used to treat a variety of ocular surface defects. Serum eye drops (SEDs) are normally produced from the patient's blood. However, not all patients can donate sufficient or suitable blood, and logistics can be challenging. Allogeneic blood from voluntary blood donors does not have these disadvantages. Our aim was to evaluate whether autologous and allogeneic SEDs have comparable efficacy and tolerability.

Methods: In a prospective, double-blind crossover trial, patients with severe dry eyes were randomized to first receive autologous SEDs for one month, followed by one-month washout, before receiving allogeneic SEDs for 1 month; or receive the SED preparations in reverse order. The Ocular Surface Disease Index (OSDI) was the primary endpoint, and various secondary endpoints were determined. A linear mixed model with random intercept for each patient was applied per treatment group to compare the pre- and postoutcome measurements.

Results: Nineteen patients were enrolled, of whom 15 completed the trial. When autologous SEDs were used, the mean $\pm$ SD OSDI improved from 62 $\pm$ 19 to 57 $\pm$ 18. For allogeneic SEDs, the OSDI changed from 59 $\pm$ 20 to 56 $\pm$ 23. The estimated mean difference (95% confidence interval) was -4.2 (-9.5 to 1.2) for autologous and -4.5 (-9.8 to 0.9) for allogeneic SEDs (both, not significant). Adverse events were mild and resolved completely.

Conclusion: Autologous and allogeneic SEDs have comparable efficacy and tolerability for use in patients with severe dry eyes. Allogeneic SEDs are therefore an attractive alternative for patients who need SEDs but are clinically or logistically unable to donate blood.

Key words: serum eye drops – severe dry eye syndrome – Sjögren disease – autologous – allogeneic

Introduction

Autologous serum eye drops (SEDs) have been used for over four decades to treat severe dry eye syndrome (Ralph 1975; Fox 1984), which is caused by a variety of diseases, such as Sjögren's syndrome and graft-versus-host disease (GvHD). Autologous SEDs have slowly found their way into clinical practice, with publications appearing since the early 2000s. A Cochrane meta-analysis was performed in 2017, which included five randomized trials evaluating the clinical effectiveness of autologous SEDs versus artificial tears or saline in patients with severe dry eye syndrome (Pan 2017). Due to the heterogeneity between the studies, the actual meta-analysis could not be performed.

While effective in treating certain patients with severe dry eye symptoms, autologous SEDs have disadvantages. Logistically, collecting blood and processing into SEDs may result in a considerable waiting time for the patient. Additionally, patient-specific conditions, such as poor venous access, an already low haemoglobin level, fear of needles, the patient's age or limited mobility may prohibit the collection of sufficient blood. Therefore, we were interested in investigating the provision of allogeneic SEDs as an alternative for such patients. Donor blood can be collected and processed in advance,

making SEDs available off the shelf. Donors are healthy by definition, in general have good venous access, and undergo a check-up prior to donating approximately 500 ml of whole blood. Donors can be further selected for specific characteristics, for example being male with no history of blood transfusion, in order to decrease the risk that HLA antibodies are present (Middelburg 2011), since these antibodies can react with corneal epithelium. As with any other use of donated blood, there are risks for the recipient, including a minimal risk of transmission of diseases, and presence of antibodies that potentially react with epitopes in the eye. Allogeneic SEDs are generally assumed to be as effective as autologous SEDs to treat severe dry eye syndrome (Chiang 2007; Chiang 2009; Na & Kim 2012; Harritshøj 2014; Hung 2019). The majority of studies with allogeneic SEDs have been performed in patients who were not responsive to regular therapy, and for whom autologous serum could not be collected or was unsuitable for use, implying that at least in these patients, a direct comparison of allogeneic with autologous SEDs is not possible. Other than the retrospective analysis of Hung (2019), to our knowledge, a prospective comparison of the clinical effectiveness of allogeneic SEDs with autologous SEDs has not been performed. Therefore, a prospective randomized double-blind crossover clinical trial was undertaken, evaluating the effectiveness and tolerability of autologous and allogeneic SEDs in reducing the symptoms of dry eye disease. The aim of the study was to compare the OSDI of patients treated with autologous and allogeneic SEDs after one month's use. Also, we evaluated the change in the OSDI compared with baseline. Secondary endpoints included the comparison of both types of SEDs in terms of tear break up time, tear production, percentage of punctate lesions, and visual acuity. Adverse events were recorded to assess tolerability.

Methods

Patient enrolment and treatment

Patients with chronic dry eye syndrome were considered eligible for participation in the study. Participants were eligible if they were at least 18 years of age, were expected to benefit from treatment with SEDs, were able to donate sufficient blood to prepare autologous SEDs and met the donor criteria of Sanquin Blood Supply (Amsterdam, The Netherlands), with the exception that the participants did not need to comply with the requirements for age, donation frequency or haemoglobin level. Patients were excluded from participation if they had corneal lesions more than punctate lesions, had a history of unstable *Herpes simplex* virus (HSV) keratitis or were treated for HSV keratitis, currently already used SEDs, were pregnant, lactating or intended to become pregnant in the next 3 months, were unable or unwilling to give informed consent, had active (systemic) microbial infection, were immuno-deficient or had poor venous access. Patients who used other topical treatments, such as glaucoma drops, were allowed to participate and to use these drops throughout the study. Ophthalmologists at the Radboud University Medical Center, Nijmegen, The Netherlands, enrolled the patients.

The SED treatment periods and the washout period all lasted one month. Patients were randomized to first be treated with autologous SEDs, followed by a washout period where they received the therapy they used before enrolment in the trial, with subsequently 1 month with allogeneic SEDs (group A), or were initially treated with allogeneic SEDs followed by the washout period, followed by treatment with autologous SEDs (group B). When using SEDs, the patients were taken off their current therapy with artificial tears. Randomization was performed with a 1-to-1 chance to be randomized in each group. The randomization list was generated in the electronic data capture software (Castor EDC, Amsterdam, The Netherlands), using a block size of four.

This single-centre study was conducted in an out-patient setting at the Department of Ophthalmology of the Radboud University Medical Center, Nijmegen, the Netherlands. Ethics approval was obtained from the hospital Commission for Research in Humans, approval number 2015–1824. Research was performed in adherence to the Declaration of Helsinki. The trial was registered at clinicaltrials.gov under number NCT03085290. All patients gave written informed consent.

Serum eye drops: production and use

After randomization, the patients were referred to the nearby blood centre to donate for the production of SEDs. For a detailed description of the autologous SED production, see Supplement 1.

Allogeneic SEDs were collected from never-transfused male repeat donors with blood group AB. This is an existing pool of dedicated donors, who are aware of the purpose of their donation, and sign a consent form acknowledging that their donation will not be used for transfusion purposes. To increase viral safety, sera were released for use if the donor returned after at least four months, and were again tested negative for all screening tests ('quarantine method'). The donation was processed in an identical fashion as autologous serum as described in the previous paragraph, with the exception that autologous units could be released immediately. Serum eye drops (SEDs) from one allogeneic serum were used to treat multiple patients in the trial.

On the day of the patient's visit, the package was inserted into a shipping container to keep the vials frozen until they arrived home for further storage at −18°C. The patient received a package of SEDs according to their randomization (autologous or allogeneic) for use in the coming month. Patients were instructed to thaw one vial for use the next day and keep the thawed vial at 4°C for the next 24 hours. Patients were directed to use the SEDs six times daily.

Observations and endpoints

At baseline, patient characteristics such as sex, age, diagnosis and current medication for the treatment of their dry eyes were recorded. Additionally, the OSDI, tear break up time, tear production, percentage punctate lesions and visual acuity were determined, as detailed below. Study endpoints were determined at the start of the trial, after one month of treatment with the first type of SED, after one-month washout and after one month of treatment with the second type of SED.

All information was entered into a database built with Castor software, a secure web-based programme that allows direct entry of relevant information into the system.

The primary objective was to compare the OSDI of autologous with allogeneic SEDs after one month of use. We also compared the OSDI from baseline to the score after 1 month of use of autologous or allogeneic SEDs. The study was designed as a pilot study; that is, a priori it was known that a comparison between autologous and allogeneic would not have sufficient statistical power to detect a difference and that only a comparison with baseline could be made. The OSDI is a validated scoring system that determines the degree of discomfort that a patient experiences (Schiffman 2000). This questionnaire consists of 12 questions asking the patient about their symptoms in the previous week, each giving a score from 0 (discomfort none of the time] to 4 (discomfort all of the time). The OSDI is calculated using the formula: ([sum of scores]*25)/(number of questions answered). Therefore, the OSDI can range from 0 (no symptoms) to 100 (severe dry eye symptoms all of the time).

There were various secondary outcomes, assessed in both eyes. During each study visit, first, visual acuity was determined. Secondly, after a drop of fluorescein dye was placed in the inferior conjunctival fornix, the 'number of punctate lesions' was estimated as the percentage of punctate lesion staining of the total corneal area. Thirdly, the tear film break up time (i.e. the time in seconds between the last blink and the occurrence of the first dry spots on the cornea) was measured. Finally, Schirmer's test was used to measure the tear production; without topical anaesthesia, a strip of filtration paper was placed on the temporal conjunctiva between closed eyelids of both eyes. After 5 min, the number of millimetres wet paper indicated the tear production of each eye.

Safety aspects

Adverse events and serious adverse events (SAEs) were registered in the Castor database and were categorized according to the type of reaction. The severity and imputability were assessed.

A Safety Committee was installed to judge each SAE in an unblinded fashion and was available to give advice on continuation of the study if there was reason to believe that the safety of patients was compromised.

Study conduct and blinding

No interim analyses were planned due to the low number of patients. There were no stopping rules. There were no changes in study design; study endpoints were predefined and did not change after the trial commenced. Autologous and allogeneic SEDs were aliquoted in identical dropper systems, so that the ophthalmologist, other hospital staff and the patient remained blinded to the treatment arm. The only way to identify the content was by the unit identification number, of which the code list was kept by the laboratory of Sanquin Blood Bank, who aliquoted the SEDs. Regular monitoring visits were performed to oversee execution of the study.

Statistical analysis

Demographics, diagnosis, baseline ophthalmologic measurements and the use of all ocular surface medication are summarized using descriptive statistics. Descriptive statistics for continuous variables include the number of observations, the mean with standard deviation (SD) or median with lower and upper quartiles (25th and 75th percentiles). Descriptive statistics for categorical data are expressed as frequency of observations and per cent.

Primary and secondary outcome measures were analysed as intention-to-treat (ITT) analysis. As a number of randomized patients immediately went off trial because no autologous serum could be collected, a modified ITT was ultimately performed, excluding these patients. The safety analysis was performed based on the treatment that the patient actually received.

A linear mixed model per treatment group was applied. The mean was modelled as a function of the period, the measurement order (i.e. pre/post) and their interaction. We tested for the carryover effect (interaction term, i.e. whether the change depended on the period). If these were not significant, they were excluded from the model. To model the correlation within each

patient, a random intercept was added. For secondary endpoints, to test for additional heterogeneity due to the measurement of individual eyes, a nested random intercept within the patient random intercept was added. Visual acuity was converted into the logarithm of the minimal angle of resolution (logMAR). Pre- and postobservations and differences between observations from the linear mixed model are reported as estimated mean and SE and estimated mean difference with 95% CI. Statistical analysis was carried out with SPSS version 23 (IBM, Armork, NY, USA).

Results

A total of 47 patients were considered for inclusion, of whom 19 were ultimately randomized, and 15 completed the trial (see Supplemental Figure S1). We failed to obtain autologous blood from four patients, one in group A and three in group B, all due to poor venous access. The remaining 15 patients all successfully concluded their participation in the trial. One patient contributed with only one eye, as the other eye was in a very poor condition. Enrolment started in June 2017 and the last patient finished the trial in October 2018. Table 1 shows their baseline characteristics, with an average age of 73 years, predominantly female, and the most common diagnosis was severe dry eye syndrome. The baseline ocular characteristics are in line with that diagnosis, with a short break up time, low tear production and the presence of corneal punctate lesions. LogMAR was on average 0.046, which is a visual acuity of 0.90 on the decimal scale.

Ocular surface disease index

Table 2 shows the OSDI of the patients before and after treatment with SEDs. At endpoint, there was no difference in OSDI between autologous and allogeneic SEDs. The estimated mean difference between pre- and post-treatment for both groups showed no statistically significant effect for either of the SEDs. As illustrated in more detail in Supplemental Figure S2, there was considerable variability in response for individual patients. Some patients showed a moderate to good response after SED use, while others showed an increase in OSDI, averaging out the

Table 1. Baseline patient characteristics of included patients.

	Patients (*n* = 15)
Sex, *n* (%)	
Female	14 (93)
Male	1 (7)
Age, mean (SD)	73 (9)
Underlying eye disease, *n* (%)	
Extreme dry eye disease	9 (60)
Sjögren's syndrome	3 (20)
Other	3 (20)
Standard Ocular Surface Medication/Therapy, *n* (%)	
Artificial tear product	13 (87)
Gel for dry eyes	6 (40)
Ointment	1 (7)
OSDI, mean (SD)	60 (19)

	Eyes (*n* = 29)
Tear break up time, s, median (IQR)	9.10 (5.75 to 12.25)
Tear production time, mm/5 min, median (IQR)	5.0 (4.0 to 12.5)
Corneal punctate lesions, %, median (IQR)	10 (0 to 55)
LogMAR, median (IQR)	0.046 (−0.039 to 0.139)

IQR = interquartile range, SD = standard deviation.

Table 2. Ocular Surface Disease Index before and after treatment with autologous and allogeneic SEDs and pre- and post-treatment differences

	Autologous SEDs	Allogeneic SEDs
n patients	15	15
OSDI pre, mean (SD)	62 (19)	59 (20)
OSDI post, mean (SD)	57 (18)	56 (23)
Estimated mean difference (95% CI)	−4.2 (−9.5 to 1.2)*	−4.5 (−9.8 to 0.9)*

CI = confidence interval, SD = standard deviation.
* not significant, $p > 0.05$.

overall response. In the autologous group, 11/15 patients showed a decrease in OSDI, compared with 9/15 patients in the allogeneic group. Most patients reacted in a similar fashion to autologous and allogeneic SEDs: 9 patients had a similar response to both preparations, while 6 patients showed an opposing response. Nonetheless, all but one patient had an OSDI > 33, indicating that all patients still met the criterion for severe dry eye disease.

Secondary endpoints

The average tear break up time showed no difference between autologous and allogeneic SEDs (Table 3). Only 10 or 9 out of 29 eyes showed an improvement for autologous and allogeneic SEDs, respectively (see Supplemental Figure S3a). For tear production, minor differences could be detected from baseline to study endpoint. Supplemental Figure S3b shows that 19 eyes treated with autologous and 11 eyes treated with allogeneic SEDs showed an increase in tear production. A small change was observed in the number of punctate lesions for autologous and allogeneic SEDs. As shown in Supplemental Figure S3c, 12 eyes in the autologous group and 14 in the allogeneic group showed a reduction in the percentage of punctate lesions, while other eyes showed an increase. In the eyes both treated with autologous or allogeneic SEDs, the logMAR on average improved somewhat. However, the difference was not statistically significant nor clinically relevant. Supplemental Figure S3d shows that in both groups, 17/29 eyes showed an improvement in logMAR.

Adverse events

Six adverse events were observed during the study period in five patients. All were minor, non-life-threatening events, of which two were judged to be possibly related to the SEDs. Both these events occurred in the same patient after using autologous as well as allogeneic SEDs. In both instances, the patient complained about dry eyes. All adverse events resolved completely. None of the reactions were considered to be SAEs. Lastly, all bacterial screenings of the SEDs were negative.

Discussion

This study investigated the effect of autologous and allogeneic SEDs in the management of patients with severe dry eye disease. We found no difference for any of the clinical parameters between autologous or allogeneic SEDs with regard to the OSDI, tear break up time, tear production, punctate lesions and visual acuity. In addition, in this cohort of 15 patients, only mild adverse events were seen, indicating that the tolerability of both SED preparations is high, with no major difference between the two.

When comparing SED treatments with the patient's baseline treatment with artificial tears, gels or ointments, some small improvement was seen in OSDI and in tear production, though not to a degree that the symptoms completely resolved. This is in line with the conclusions of the two recent meta-analyses, which both showed a small advantage of the use of SEDs over artificial tears when treating patients with severe dry eyes (Pan 2017; Franchini 2019). Serum eye drops are known to be the most effective in patients with an even more serious condition, such as GvHD (Ogawa 2003; Chiang 2007; Na & Kim 2012; Tahmaz 2017), Stevens-Johnson syndrome (Tsubota 1996) or chemical burns (Salman & Gündoğdu 2010; Semeraro 2014). However, such patients were not eligible for our cross-over study that includes a washout phase, as withholding SED treatment is considered unethical for patients with these conditions.

The patients in our cohort were already on treatment for their symptoms. If newly diagnosed patients had been enrolled, the beneficial clinical effect of SEDs may have been more pronounced. However, patient recruitment would have been problematic as naïve patients are fairly rare, and, in a crossover design type of study, the patients would not truly be naïve in the second phase of the study,

Table 3. Estimated secondary outcome measures before and after treatment with autologous and allogeneic SEDs.

	Autologous SEDs	Allogeneic SEDs
n patients/n eyes	15/29	15/29
Tear break up time, s		
Pre, estimated mean (SE)	8.5 (0.6)	7.2 (0.5)
Post, estimated mean (SE)	8.4 (0.7)	7.5 (0.6)
Estimated mean difference (95% CI)	−0.11 (−1.4 to 1.2)	0.21 (−0.9 to 1.3)
Tear production time, mm/5min		
Pre, estimated mean (SE)	5.9 (0.8)	9.7 (1.5)
Post, estimated mean (SE)	7.5 (0.8)	8.2 (1.2)
Estimated mean difference (95% CI)	1.55 (0.32 to 2.8)	−1.6 (−3.6 to 0.49)
Corneal punctate lesions, %		
Pre, estimated mean (SE)	19 (3)	26 (5)
Post, estimated mean (SE)	21 (5)	22 (5)
Estimated mean difference (95% CI)	2 (−5 to 9)	−3 (−12 to 5)
LogMAR		
Pre, estimated mean (SE)	0.009 (0.280)	0.090 (0.040)
Post, estimated mean (SE)	−0.035 (0.230)	0.017 (0.031)
Estimated mean difference (95% CI)	−0.044 (−0.90 to 0.001)	−0.073 (−0.110 to 0.036)

CI = confidence interval, SE = standard error.

introducing a period effect. Because patients already received treatment with artificial tears, gels or ointments, the decision to join our study could stem from not being satisfied with their current treatment. This could preselect to a group of patients who are difficult to treat, thereby introducing a bias.

Six adverse events were observed in five patients, of which two were possibly attributable to the use of SEDs. Side effects occurred in similar frequencies in patients treated with either autologous or allogeneic SEDs. No SAEs were observed in this study. Serious adverse events (SAEs) reported for patients using SEDs are rare, and a much larger study will be needed to determine how often they occur.

For the current study, all blood donations were tested for the presence of human immunodeficiency virus (HIV), hepatitis-B, hepatitis-C and hepatitis-E virus and *Treponema pallidum*. The risk of transmission is extremely low (<1:5 × 10^5 for hepatitis-B and even lower for the other pathogens), but the risk must be balanced against the benefits and risks of autologous SEDs. Nonetheless, for an ongoing trial with allogeneic SEDs (AmuSED study, NCT03539159), we additionally test for herpes simplex virus type 1 and herpes simplex virus type 2, Varicella zoster virus and cytomegalovirus, as a precautionary measure.

Overall, no significant differences were observed whether patients were treated with autologous or allogeneic SEDs. Our prospective findings support those of the previously published retrospective data that showed effectiveness and safety of allogeneic SEDs (Chiang 2007; Chiang 2009; Na & Kim 2012; Harritshøj 2014). Further, our findings are similar to those of Hung (2019), who published a retrospective crossover study and also demonstrated no difference between autologous or allogeneic SEDs.

The current pilot study gives direction where future research is needed. Our study suggests that there are patients that respond, and patients that do not respond to SEDs, and it is worthwhile to determine whether there is an underlying common factor. Also, considering generalizability of the outcomes of the current trial, patients with other diagnoses (such as Stevens-Johnson syndrome, trauma, alkali or acid burns or Laser-assisted In Situ Keratomileusis (LASIK)) may benefit from allogeneic SEDs, and this also warrants further study. Our aforementioned follow-up study with 54 patients, a comparison of the Meise dropper system with the Mu-Drop system, both with allogeneic SEDs, will shed light on some of these questions.

In conclusion, our data indicate that autologous and allogeneic SED have comparable efficacy and tolerability for use in patients with severe dry eyes. In this study, not all patients benefitted equally from the use of SEDs over standard ocular surface therapy.

Allogeneic SED may provide an attractive alternative for patients who need SEDs but are logistically or clinically unable to donate blood.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram showing patient inclusion, treatment and analysis.

Figure S2. Individual Ocular Surface Disease Indices before and after treatment with autologous and allogeneic SEDs.

Figure S3. Individual secondary outcome measures before and after treatment with autologous and allogeneic SEDs.